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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
BERTAGNA, ANGELA MARIE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,544	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,12-17,19-25,34-51,57 and 58* is/are pending in the application.

4a) Of the above claim(s) *34-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12-17,19-25,57 and 58* is/are rejected.

7)☒ Claim(s) *10,12,17,23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on November 20, 2008 is acknowledged. Claims 9, 10, 12-17, 19-25, 34-51, 57, and 58 are currently pending. In the response, Applicant amended claims 9, 12, 17, 19, and 20 and canceled claims 1-8, 11, 18, 26-33, and 52-56. Claims 34-51 remain withdrawn from consideration as being drawn to a non-elected invention.

The following are new grounds of rejection. Any previously made rejections or objections not reiterated below have been withdrawn in view of the claim amendments. Applicant's arguments that remain pertinent to the new grounds of rejection presented below have been fully considered, but they were not persuasive for the reasons below. Since the new grounds of rejection were necessitated by Applicant's amendment, this Office Action is **FINAL**.

Claim Objections

2. Claims 10, 12, 17, 23, and 24 are objected to because of the following informalities:

(a) Claim 10 appears to be missing the word "and" after the words "full-length cDNA".

(b) Reversing the order of the clauses "comprising the steps of" and "wherein the region includes the most 5' end of the mRNA" in lines 2-3 of claim 12 is suggested to improve the clarity of the claim.

(c) Claim 17 appears to contain a typographical error. It would appear that "synthesized in step (ii)" was intended for "synthesized in step (iii)" appearing in step (iv).

(d) Claim 23 is grammatically incorrect. Replacing the word "the" appearing before the words "Class II" with the word "a" is suggested.

(e) Claim 24 is grammatically incorrect. It appears to be missing text, such as "selected from", after the words "the restriction enzyme is".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 10, 12-17, 19-25, 57, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 10, 13, 16, and 57 are indefinite, because independent claim 9 contains steps directed to the manipulation of RNAs (see (i) - (iii)) and steps directed to the manipulation of mRNAs (see (a), (c), and (d)). As a result, the relationship between the RNAs and mRNAs manipulated during the method is unclear.

Claims 9, 10, 13, 16, and 57 are also indefinite, because independent claim 9 recites the limitation "the 5' end of an mRNA" in steps (a), (c), and (d). There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for "the most 5' end of the mRNA".

Claims 12, 14, 15, and 58 are indefinite, because independent claim 12 contains steps directed to the manipulation of RNAs (see (i) - (iii)) and steps directed to the manipulation of mRNAs (see (a), (iv), (c), and (d)). As a result, the relationship between the RNAs and mRNAs manipulated during the method is unclear.

Claims 12, 14, 15, and 58 are also indefinite, because independent claim 12 recites the limitation "the 5' end of an mRNA" in steps (a), (iv), (c), and (d). There is insufficient antecedent basis for this limitation in the claim. There is sufficient antecedent basis for "the most 5' end of the mRNA".

Claims 17 and 19-25 are indefinite, because independent claim 17 recites the limitation "the 5' end of an mRNA" in steps (a), (i), (c), and (d) and the limitation "the mRNA having the linker" in step (ii). There is insufficient antecedent basis for these limitations in the claim. There is sufficient antecedent basis for "the most 5' end of the mRNA".

Claims 17 and 19-25 are indefinite, because independent claim 17 recites "a second cDNA" in step (iv). Since no mention is made in the claim of "a first cDNA", there is uncertainty as to the completeness of this claim.

Claims 19-22 are further indefinite, because claim 19 recites the limitation "the second-strand cDNA" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 20-22 are further indefinite, because claim 20 recites the limitation "the recovering step" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 17, 19-21, and 23-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Pedersen (US 2003/0113737 A1; cited previously).

These claims are drawn to a method for preparing a DNA fragment corresponding to the 5' end of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 17, Pedersen teaches a method for preparing a DNA fragment comprising a nucleotide sequence that corresponds to the 5' end of an mRNA comprising:

(a) preparing a nucleic acid that corresponds to a nucleotide sequence of the 5' end of an mRNA (see Figure 12, steps I & II and paragraphs 61, 254 and 261-262, where the decapped mRNA is prepared)

(b) attaching at least one linker to the nucleic acid by:

(i) attaching a linker to an end region corresponding to the most 5' end of the mRNA, wherein the linker contains a recognition sequence for a restriction enzyme that cleaves at a site different from its recognition sequence (see Figure 12, step III and paragraphs 61, 254 and 261-262, where the adapter, which has recognition sequences (A) and (B) for a nicking endonuclease and a Type IIS restriction enzyme, respectively, is ligated to the 5' end of the decapped mRNA)

(ii) synthesizing a nucleic acid using the mRNA having the linker attached as a template (see Figure 12, step IV and paragraphs 61, 254 and 261-262, where reverse transcription using random decamers is taught)

(iii) removing the mRNA (see Figure 12, step V and paragraphs 61, 254 and 261-262, where the second strand synthesis step inherently removes the mRNA (*e.g.* by displacement)

(iv) synthesizing a second strand cDNA using the nucleic acid of step (ii) as a template (see Figure 12, step V and paragraphs 61, 254 and 261-262)

(c) cleaving the nucleic acid with the Type IIS restriction enzyme and the nicking enzyme (paragraph 263)

(d) collecting the resulting fragment corresponding to the most 5' end of the mRNA (see paragraph 263; Figure 12 and paragraph 61 teach that the cleavage with the nicking enzyme and the Type IIS restriction enzyme as described in paragraph 263 generates a fragment corresponding to the 5' terminus of the mRNA).

Regarding claim 19, Pedersen teaches that the second strand cDNA is synthesized using a primer that has the sequence of the linker (paragraphs 61 and 261). These primers are inherently partially complementary to the linker region (*i.e.* they contain at least 2 consecutive nucleotides that are complementary to the linker region - see pages 30-33 for specific examples of such adapters).

Regarding claims 20 and 21, Pedersen teaches that a selective binding substance, specifically biotin, is attached to the oligonucleotide primers used to synthesize second strand cDNA and that the products of the second strand synthesis reaction are recovered using a solid support having streptavidin immobilized thereupon (see paragraphs 262 and 791).

Regarding claims 23-25, Pedersen teaches that the restriction enzyme is a Class IIS restriction enzyme (see paragraphs 61, 254, and 262-263), such as Bpm I (paragraphs 785 & 791) or BsgI (page 31).

Response to Arguments:

Applicant's arguments filed on August 4, 2008 have been fully considered, but they were not persuasive. Applicant first argues that Pedersen does not teach all of the elements of the amended claims, specifically the requirement for isolation of a DNA fragment corresponding to the 5' terminus of an mRNA molecule (see page 12). Applicant also argues that the claim 17 as amended incorporates the limitations of claim 18, which was not previously rejected as being anticipated by Pedersen (see page 12).

Applicant's first argument was not persuasive, because as discussed above, Pedersen teaches a method for isolating a DNA fragment corresponding to the 5' terminus of an mRNA molecule (see Figure 12 and paragraphs 61, 254, and 261-263 cited above, where the DNA fragment produced by digestion with the nicking enzyme and the Type IIS endonuclease includes a region corresponding to the 5' terminus of the mRNA). Applicant's second argument was also unpersuasive, because the limitations recited in claim 18 (*i.e.* that the linker contains a double-stranded oligonucleotide region and that the second strand cDNA is synthesized using the linker) do not appear to have been incorporated into independent claim 17. The linker recited in amended claim 17 is required to contain at least one recognition site for a restriction enzyme that cleaves at a site different from its recognition site. The method of Pedersen utilizes a linker having these features (see Figure 12, paragraph 61, and paragraphs 261-263). Amended claim

17 also requires the second strand synthesis step to be conducted using the linker as a template (see step iv). The method of Pedersen also comprises this step (see Figure 12, paragraph 61, and paragraphs 261-263). In contrast to Applicant's arguments, the linker recited in amended claim 17 is not required to contain a double-stranded region. Since Applicant's arguments were not persuasive, the rejection under 35 U.S.C. 102(e) has been maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 2003/0113737 A1; cited previously) in view of Cocuzza et al. (US 5,484,701; cited previously).

Pedersen teaches the method of claims 17, 19-21, and 23-25, as discussed above.

Pedersen teaches that the oligonucoleotide primer used in the second strand cDNA synthesis step contains biotin to permit streptavidin-mediated capture rather than digoxigenin to permit capture with an anti-digoxigenin antibody (see above).

Cocuzza teaches a method for isolating primer extension products prior to electrophoresis comprising biotinylation of the primer extension product and isolation with a support-immobilized avidin (abstract and column 3, line 55 – column 4, line 20). Regarding claim 22, Cocuzza teaches that biotinylated primer extension products may also be isolated using an antibody-antigen capture system, wherein the antigen digoxigenin is attached to the primer and the primer extension products are captured with a support-immobilized anti-digoxigenin antibody (column 7, lines 28-43). In this passage, Cocuzza further teaches that this system performs as well as the biotin-avidin system, and that methods for immobilizing antibodies on solid supports are known.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the biotin-streptavidin capture method taught by Pedersen with the digoxigenin-anti-digoxigenin antibody capture method taught by Cocuzza. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43). As noted in MPEP 2144.06, substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious. Thus, the method of claim 22 is *prima facie* obvious over Pedersen in view of Coccuza.

Response to Arguments:

Applicant's arguments filed on August 4, 2008 have been fully considered, but they were not persuasive. Applicant first argues that the teachings of Cocuzza do not remedy the deficiencies of Pedersen with respect to independent claim 17 (pages 19-20). This argument was not persuasive, because as discussed above, Pedersen teaches all of the elements of independent claim 17. As discussed above, in contrast to Applicant's arguments, amended claims 17 and 22 do not require a double-stranded linker which is then used to prime second strand cDNA synthesis.

Applicant also argues that the Cocuzza reference is non-analogous art (see page 19). In response to this argument, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In the instant case, the teachings of Cocuzza regarding the use of digoxigenin-mediated purification of nucleic acids compared to biotin-avidin purification systems would have been reasonably pertinent to the problem with which Applicant and Pedersen was concerned, namely the use of a specific binding pair (*e.g.* biotin-avidin or digoxigenin) for nucleic acid purification. Therefore, the Cocuzza reference is not considered to be non-analogous art.

Applicant also argues that there is no motivation to combine the teachings of Cocuzza and Pedersen (page 20). In response this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either

in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, as discussed above, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43), an ordinary artisan would have been motivated to substitute one nucleic acid purification method for the other with a reasonable expectation of success. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, no evidence has been presented to suggest that substitution of the biotin-avidin system taught by Pedersen for the digoxigenin system of Cocuzza is associated with unexpected results, and therefore, the substitution of these art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious. Since Applicant's arguments were not persuasive, the rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Pedersen in view of Cocuzza has been maintained.

8. Claims 9, 10, 12, 14-16, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited previously) in view of Carninci et al. (Genomics (1996) 37: 327-336; cited previously).

These claims are drawn to a method for preparing a DNA fragment corresponding to the 5' end of an mRNA.

Kinzler teaches a method for preparing DNA fragments corresponding to the 5' end of an mRNA (see column 4, lines 33-41, column 4, lines 47-50, and column 4, lines 65 - column 5, line 12). Regarding claims 9, 10, 12, 14, and 15, the method of Kinzler comprises:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA by:

(i) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (column 4, lines 1-7)

(ii) recovering a nucleic acid that corresponds to the 5' end of the mRNA from the cDNA/RNA hybrids (column 4, line 47 – column 5, line 11).

(b) attaching at least one linker to the nucleic acid (see Figure 1A and column 4, line 47 - column 5, line 50, where linkers are ligated to the 5' end after cleavage with the "anchoring enzyme")

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of an mRNA (see Figure 1A and column 5, lines 45-60, where cleavage with the Type IIS "tagging enzyme" is taught)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (see Figure 1A-1B and column 6, line 10 - column 7, line 67).

Further regarding claims 9, 10, 12, 14, and 15, Kinzler teaches that the 5' cap of the newly synthesized cDNA can be utilized for labeling or binding a capture means for isolation of

a 5' defined nucleotide sequence tag (column 5, lines 7-11). However, Kinzler does not teach conjugation of a selective binding agent to the 5' cap of the mRNA.

Regarding claims 10, 14-16 and 58, Kinzler teaches that the cDNA may be labeled with selective binding substances such as biotin and digoxigenin for capture by the matching binding substances streptavidin and an anti-digoxigenin antibody, respectively (column 5, lines 7-11). Kinzler also teaches the use of magnetic streptavidin-coated beads for capture (column 9, lines 15-18).

Carninci teaches a high efficiency method ("CAP trapper") for isolating full-length cDNA molecules (see Figure 1 and pages 328-329).

Regarding claim 9, the method of Carninci comprises synthesizing first strand cDNAs using RNA as a template and producing cDNA/RNA hybrids of the resulting first-strand cDNAs and the RNAs (page 328, column 1 "First-strand cDNA preparation" and Figure 1), selecting a particular cDNA/RNA hybrid that has the 5' cap structure of the mRNA using a selective binding substance which specifically recognizes the 5' cap structure (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads), and recovering a nucleic acid corresponding to the 5' end of the mRNA (page 328, "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Regarding claim 10, Carninci teaches preparation of a full-length cDNA using the method described above (see abstract and page 328, column 2). Carninci further teaches that the selective binding substance is attached to a support (page 328, column 2, where the selective binding substance is magnetic beads coated with streptavidin).

Regarding claim 12, the method of Carninci comprises:

(a) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (page 328, column 1 "First-strand cDNA preparation" and Figure 1)

(b) conjugating a selective binding substance to a 5' cap structure of an mRNA present in the RNAs, thereby extending the 5' (page 328, column 2, "Biotinylation of diol groups of RNA"; see also Figure 1)

(c) contacting the cDNA/RNA hybrids with a support, wherein another matching selective binding substance is fixed to the support, and the matching selective binding substance (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin-coated magnetic beads)

(d) recovering the a nucleic acid corresponding to the 5' end of the mRNA from the mRNA fixed to the support (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads).

Regarding claims 14, 16, and 58, Carninci teaches that the selective binding substance is biotin and that the matching binding substance is streptavidin. Carninci further teaches that the streptavidin is coated on magnetic beads (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Carninci teaches, "The overall efficiency and yield of the full-length cDNA is thus far superior to other conventional methods for the preparation of full-length cDNA libraries. Our

method allows the preparation of high-content full-length cDNA libraries, even from relatively small quantities of tissues or early embryos, with no bias in representation since no PCR amplification step has been introduced (page 328, col. 1)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate the CAP trapper method taught by Carninci into the method of Kinzler. As discussed above, one application of the method taught by Kinzler was to generate sequence tags from the 5' end of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Carninci taught that conventional reverse transcription protocols often generate a high percentage of truncated products (page 327) and further taught an extremely efficient, high-yield method for selecting full-length transcripts (see page 328 cited above), an ordinary artisan would have been motivated to attach a biotin molecule to the mRNA template as suggested by Carninici prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to generate 5' end-specific sequence tags using the method of Kinzler. Increasing the number of full-length cDNA molecules in the pool prior to restriction enzyme digestion and generation of tags would have improved method taught by Kinzler by increasing its ability to identify novel sequences in the 5' region of an mRNA sample. Finally, since Kinzler expressly taught use of the 5' cap structure for capture of 5' end regions (see column 5, lines 7-11), an ordinary artisan would have expected a reasonable level of success in incorporating the CAP trapping procedure of Carninci into the method of Kinzler. Thus, the methods of claims 9, 10, 12, 14-16, and 58 are *prima facie* obvious over Kinzler in view of Carnici.

Response to Arguments:

Applicant's arguments filed on August 4, 2008 have been fully considered, but they were not persuasive. Applicant first argues that Kinzler only suggests isolation of sequences resulting from cleavage from the 5' end with a restriction endonuclease and that these sequences are unlikely to include a nucleic acid sequence corresponding to the 5' terminus of an mRNA as required by the claims (see pages 13-14). This argument was not persuasive, because the rejection is based on the combined teachings of Carnici and Kinzler. As discussed above, application of the teachings of Carnici to the method of Kinzler results in isolation of a nucleic acid corresponding to the 5' terminus of an mRNA.

Applicant also argues that the method of Kinzler cannot produce DNA fragments corresponding to the 5' terminus of an mRNA molecule, because the method uses two endonuclease digestion steps, the first of which cleaves within a cDNA molecule (page 14). This argument was not persuasive, because application of the teachings of Carnici regarding capturing the 5' mRNA cap, would result in a method wherein an mRNA molecule is captured via its 5' terminus onto a solid support, cleaved with a first enzyme (*i.e.* an anchoring enzyme), ligated with a linker having a Type IIS restriction enzyme site at the end cleaved by the first enzyme, and cleaved with a Type IIS restriction enzyme to produce a 5' end tag. Since Kinzler teaches that the 5' tags may include the 5' terminus of an mRNA molecule (see columns 4-5), an ordinary artisan would have had a reasonable expectation of success in selecting first and second enzymes that would permit isolation of a DNA tag corresponding to the 5' terminus of an mRNA molecule.

Applicant also argues that the Carnici reference is directed to a method for constructing high-content full-length cDNA libraries and does not teach or suggest using the 5' cap structure in a method for preparing a DNA fragment corresponding to the 5' terminus of an mRNA molecule (page 14). This argument was not persuasive, because the rejection is based on the combined teachings of Carnici and Kinzler. As discussed above, since Kinzler taught one application of the method taught by Kinzler was to generate sequence tags from the 5' end of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Carninci taught that conventional reverse transcription protocols often generate a high percentage of truncated products (page 327) and further taught an extremely efficient, high-yield method for selecting full-length transcripts (see page 328 cited above), an ordinary artisan would have been motivated to attach a biotin molecule to the mRNA template as suggested by Carninici prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to generate 5' end-specific sequence tags using the method of Kinzler.

Applicant also argues that there are secondary considerations that render the claimed methods non-obvious. Specifically, Applicant argues that the ability to obtain information regarding the 5' end of mRNA transcripts or to analyze the promoter region is a secondary consideration of non-obviousness (see page 15). This argument was not persuasive, because the ability to analyze promoter regions or the 5' end of mRNA transcripts necessarily results from the combined teachings of Kinzler and Carnici. Since Kinzler taught that analysis of 5' tags was an embodiment of the invention (columns 4-5), the ordinary artisan would have recognized that such tags would permit analysis of regions such as the 5' end of mRNA transcripts or promoter

regions. It is also noted that the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Finally, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (see page 16), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Since Applicant's arguments were not persuasive, the rejection of claims 9, 10, 12, 14-16, and 58 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Carnici has been maintained.

9. Claims 13 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited previously) in view of Carninci et al. (Genomics (1996) 37: 327-336; cited previously) and further in view of Edery et al. (Molecular and Cellular Biology (1995) 15(6): 3363-3371; cited previously) and further in view of Das et al. (Physiological Genomics (2001) 6: 57-80; cited previously).

The combined teachings of Kinzler and Carninci result in the method of claims 9, 10, 12, 14-16, and 58 as discussed above.

Neither Kinzler nor Carninci teaches that the selective binding substance is a cap-binding protein or a cap-binding antibody.

Edery teaches a method ("CAPture") of isolating full-length cDNA transcripts based on affinity capture using the cap-binding protein eIF-4e (see abstract). The method of Edery comprises the following steps: reverse transcription of mRNA to generate a cDNA/RNA hybrid, RNase A treatment, binding of eIF-4e to the 5' cap structure of the mRNA to selectively bind full-length RNA/cDNA hybrids, and binding of the eIF-4e/RNA/cDNA complex to anti-eIF-4e conjugated to sepharose beads (see Methods section, page 3364, column 2 – page 365, column 1).

Das presents a review of methods for obtaining full-length cDNA molecules. Das compared affinity selection methods taught by Carninci (cap trapper) and Edery (affinity selection using the cap-binding protein eIF-4e) and reported that the Carninci method was not specific. Specifically, Das stated:

> [I]f we compare the ability of cap trapper to discriminate between cDNA duplex with capped mRNA (generated *in vitro*) or duplexed with uncapped mRNA (generated *in vitro*), then we are unable to obtain specific selection of capped over uncapped transcripts (J. Pelletier, data not shown). This is likely due to the fact that biotin-hydrazide can also react with unoxidized RNA due to incipient reaction of cytosine residues. Hence, addition of biotin is not solely directed toward the cap structure. Also, it is important to note that the oxidation reaction with $NaIO_4$ is difficult to control, and the molar ratio of periodate to substrate is important, otherwise one gets destruction of base rings (page 73).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the affinity selection method of Edery for the cap trapper method taught by Carninci in the method resulting from the combined teachings of Kinzler and Carninci. As discussed above, Edery taught a method for isolating full-length cDNA molecules comprising affinity purification using the cap-binding protein eIF-4e (see above). An ordinary artisan would have been motivated to substitute the affinity selection method of Edery for the cap trapper

method of Carnici, since Das taught that the affinity selection method was more specific and did not involve the use of the potentially RNA-degrading reagent $NaIO_4$ (see above). Thus, the methods of claims 13 and 57 are *prima facie* obvious over Kinzler in view of Carnici and further in view of Edery and further in view of Das.

Response to Arguments:

Applicant's arguments filed on August 4, 2008 have been fully considered, but they were not persuasive. Applicant argues that the teachings of Edery and Das do not remedy the inability of the combined teachings of Kinzler and Carnici to render obvious the methods of claims 9, 10, 12, 14-16, and 58 (see page 17). This argument was not persuasive, because as discussed above, the combined teachings of Kinzler and Carnici render obvious the methods of claims 9, 10, 12, 14-16, and 58. The Edery and Das references are only cited for those teachings relevant to dependent claims 13 and 57. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Conclusion

10. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amb

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637